

Vitamin C intake and susceptibility to the common cold - Reply to comments**Hemilä H****British Journal of Nutrition** 1997; 78, 861-866Published version of the Comments and Reply: <http://dx.doi.org/10.1079/BJN19970201>**The original paper – which is being commented on – is available as a scanned version at:**http://www.ltdk.helsinki.fi/users/hemila/H/HH_1997_BJN.pdf<http://www.ncbi.nlm.nih.gov/pubmed/9059230>**This is a manuscript version of the Reply by Hemilä****Links to fulltexts and abstracts of references were added when such were identified**

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Reply by Hemilä:

Dr Bates makes five specific criticisms of my recent paper (Hemilä, 1997a) to which I shall respond separately:

1. When a person carries out twenty different subgroup analyses and finds that only one yields a statistically significant result ($P \leq 0.05$), the finding must be interpreted very cautiously as it is likely to be caused by chance alone. However, to use the same logic to explain the P value in my Table 2 for the British male studies would imply that I had carried out some 1,000,000 kinds of selections of vitamin C studies and simply picked the best one. Such an explanation of the small P value is improbable in the extreme.

A highly significant difference in common cold incidence between vitamin C and placebo groups ($P = 0.00003$) was also found in a meta-analysis of three randomized double-blind trials involving subjects under heavy acute physical stress (Hemilä, 1996a). Furthermore, a diet deficient in vitamin C increases the susceptibility of guinea pigs to infections, and in several controlled studies with human subjects vitamin C supplementation had effects on infections other than the common cold (Hemilä, 1997b,c). Thus the British male studies do not constitute an isolated group inconsistent with all other available data, but form one piece in a larger mosaic indicating that vitamin C influences the function of the immune system.

2. In examining the results of several studies on the same topic concurrently the direction of the effect being considered must be decided on, and one-tailed P values are thus appropriate (Rosenthal, 1978; Wolf, 1986). For example, if one study finds a decrease and another finds an increase in the same phenomenon, it makes no sense to compare the two studies on the basis of two-tailed P values. If there are results pointing strongly in opposite directions there is obviously no wisdom in combining them formally or informally. Nevertheless, I am not aware of studies in which a significantly higher number of colds was observed in a group administered vitamin C.

In my paper I provided confidence intervals (CI) as a measure of precision and not as a test of the null hypothesis. One-tailed $P = 0.05$ corresponds to two-tailed $P = 0.10$, which itself corresponds to the 90 % CI with one limit at the null hypothesis level (Altman, 1991). While the 95% CI is most commonly used and the 90% CI is slightly narrower, the difference has no practical relevance in my tables.

3. In a long-lasting controversy, positive and negative findings are both newsworthy. For example, while Glazebrook & Thomson (1942), Walker *et al.* (1967), Carson *et al.* (1975), Elwood *et al.* (1976)

and Tyrrell *et al.* (1977) all explicitly drew rather negative conclusions as to their findings on vitamin C and the common cold, the papers were nevertheless written and published.

The possible role of publication bias can be quantified by calculating the fail-safe N , which refers to the number of similar studies finding no difference which should remain unpublished with the effect of collectively reversing the conclusion that a statistically significant difference exists (Rosenthal, 1979; Light & Pillemer, 1984; Wolf, 1986). In the case of the four male studies in my Table 2, the fail-safe n is 31 unpublished studies finding no difference. Although this kind of measure is imprecise, publication bias seems not to be of major concern. Finally, it seems incomprehensible that publication bias would generate the substantial difference between the sexes.

4. There is only a slight difference between the two male groups of Baird *et al.* (1979) who were administered 80 mg vitamin C/d, and the difference is not in favour of orange juice. The number of cold episodes was ninety-one and ninety-three among the male subjects administered 80 mg/d in orange juice (n 62) and in synthetic drink (n 71) respectively, yielding $RR = 0.89$ (95% CI: 0.67, 1.19) in favour of the synthetic drink. Since the difference is small and statistically insignificant, it seems appropriate to combine the two groups who were administered the same vitamin C dose. The comparison between the synthetic drink containing 80 mg vitamin C/d and the synthetic drink lacking the vitamin yields $RR = 0.59$ (95 % CI: 0.45, 0.77) for males, which is essentially the same as in my Table 2.

Bates claims that the incidence of colds was extraordinarily high in the study by Charleston & Clegg (1972), but the data in my Tables 1 and 2 contradict such a suggestion. The incidence rate was 6.2/year in the Charleston & Clegg (1972) male placebo group, but 11.2/year in the Baird *et al.* (1979) male placebo group and 7.2/year in the Elwood *et al.* (1976) female placebo group. The incidence was also higher in the large-scale trials by Ludvigsson *et al.* (1977) and Pitt & Costrini (1979).

Since there is evidence indicating that the effects of vitamin C on the immune system are based on its antioxidant role (Hemilä, 1992a, 1997b), the L- and D-isomers may both affect the immune system. In particular, Bissell *et al.* (1980) found similar suppression of viral replication in cell culture with L- and D-ascorbic acid. Accordingly, in the current state of knowledge it seems reasonable to combine the Clegg & Macdonald (1975) L- and D-isomer groups.

I do not discount the study by Glazebrook & Thomson (1942). As a form of sensitivity analysis I tested the effect of excluding their study as it is technically the most deficient among those in Table 2. However, the exclusion did not reduce the difference between the vitamin C and control groups, but made it greater. The Glazebrook & Thomson trial does have shortcomings but I see no reason to disregard it. The authors explicitly paid careful attention to the comparability of the study groups. Neither does it seem likely that vitamin C added to food in a kitchen would generate a substantial

placebo effect in the dining hall. Furthermore, they did find a statistically significant decrease in the number of colds in their vitamin C group ($P = 0.048$; one-tailed χ^2 -test).

Finally, Bates's commentary ignored the randomized double-blind trial by Tyrrell *et al.* (1977) which found a significant decrease in the number of men with recurrent colds when vitamin C was administered during their first cold episode ($P = 0.018$; one-tailed χ^2 -test).

5. Since what is biologically plausible depends upon the biological knowledge of the day, the understanding of a physiological mechanism usually is not crucial in drawing inferences on causal relationships in epidemiology. For example, the notion that smoking causes lung cancer was originally derived from observational epidemiological studies and the earliest conjectures on the biological mechanism were completely erroneous (Hennekens & Buring, 1987). Moreover, it took some five decades after the emergence of the first epidemiological findings before a direct aetiological link between smoking and lung cancer could be shown at the biochemical level (Denissenko *et al.* 1996).

Nevertheless, in my paper I explicitly cite studies reporting effects of vitamin C on the immune system and there are several other similar publications (Hemilä, 1997*b*). Bates' opinion that the mechanism whereby vitamin C might affect susceptibility to infections is merely speculative misses the point entirely.

The biochemical mechanism whereby vitamin C deficiency produces the pathological defects in scurvy is not well understood, and in particular the usual textbook reference to poor hydroxylation of collagen is a gross oversimplification, if valid at all (Englard & Seifter, 1986). However, I do not think it would be appropriate to describe the present understanding as purely speculative or to conclude that vitamin C has no effect on scurvy because the biochemistry has not yet been completely elucidated.

After his specific criticisms, Bates offered some general opinions on nutritional recommendations. He suggested that the effects of micronutrients should be considered primarily in the light of human intervention studies, a viewpoint which I heartily endorse. However, such an approach has not been applied in the official monographs on these issues.

In the British recommendations no mention is made of the vitamin C and common cold link (Department of Health, 1991) although more than sixty intervention studies have been published on the issue (Kleijnen *et al.* 1989). In fact, one of the studies cited in the UK recommendations reported that the geometric mean duration of colds was 6.4 days in vitamin C-deprived subjects and 3.3 days in non-deprived subjects, and the authors concluded that the absence of vitamin C tended to cause colds to last longer (Bartley *et al.* 1953). The brief comment on the vitamin C and plasma cholesterol relationship is based on one single uncontrolled study (Department of Health, 1991) although over thirty intervention studies have been published, eleven of which were placebo-controlled

(Hemilä, 1992*b*).

The lack of thoroughness in reviewing the literature is not a problem restricted to the UK recommendations but is also apparent in the US recommendations (National Research Council, 1989). For example, the conclusion that vitamin C has no meaningful effect on the common cold is based on the reviews by Chalmers (1975) and by Dykes & Meier (1975). However, both reviews contain serious errors which should have been recognized by the authors of the monograph had they been familiar with the intervention study reports (Hemilä & Herman, 1995; Hemilä, 1996*b*). The conclusion that vitamin C has no effect on cholesterol metabolism is based on a single uncontrolled study (National Research Council, 1989) and no reference is given to the placebo-controlled trials, some of which reported a significant difference between the vitamin C and placebo groups (Hemilä, 1992*b*, 1993).

Because of the prominent political dimension of the nutritional recommendations there is evidently considerable incentive to oversimplify these complex issues and to be conservative as regards new findings. In the popular literature there are numerous, obviously false, claims about the benefits of vitamin C supplementation and such claims are utilized commercially; in this respect a conservative attitude in the nutritional recommendations is understandable. Nevertheless, such political concerns should not bias investigation of the actual scientific questions and provide no valid reason to ignore the intervention studies examining the effect of vitamin C on the common cold and on plasma cholesterol level, and a large number of intervention studies on other topics, some of which were reviewed by Basu & Schorah (1982). Furthermore, when a large number of studies have examined the same issue there is considerable risk that important points are not recognized easily, which underscores the importance of a systematic approach (Light & Pillemer, 1984; Wolf, 1986). However, in the case of vitamin C a systematic method of reviewing the literature was not applied (National Research Council, 1989; Department of Health, 1991).

As regards the safety of vitamin C supplementation, much speculation about potential harm has been advanced, but it has been shown to be unfounded (Rivers, 1987; Marks, 1989; Hemilä, 1994; Bendich & Langseth, 1995). Since none of the common cold studies (Hemilä 1992*a*) in which 1–3 g vitamin C/d was regularly administered to over 3000 subjects in all reported any meaningful difference in the occurrence of adverse symptoms between the vitamin and placebo groups, the safety of vitamin C in the 0.1–1 g/day range is no real concern. Obviously, argument for higher intakes cannot be based on safety alone, but must include sound evidence of benefit.

There are findings suggesting that in doses higher than those officially recommended, vitamin C may be beneficial for certain population groups as regards conditions other than scurvy. Nevertheless, we have no real understanding of who these subpopulations are, what the magnitude of the effect is, and what kind of dose would be best. If the subpopulations are small there is no point in recommending higher intakes for the general population. Table 1 of my paper indicates that the British male studies

should not produce over-optimism as to the effect of vitamin C on the incidence of colds (Hemilä, 1997*a*). The effect of vitamin C on the symptoms of colds has usually been modest (Hemilä, 1992*a*). Nonetheless, the common cold is such a ubiquitous ailment that even quite a modest effect may be worth exploitation, and it is possible that there are effects on other conditions to be considered (Stone, 1972; Basu & Schorah, 1982; Hemilä, 1992*b*; Bielory & Gandhi, 1994; Bendich & Langseth, 1995; Hemilä, 1997*b,c*).

The possibility of publication bias and various technical shortcomings in the published studies should not discourage us from planning and carrying out carefully designed trials which address these questions more explicitly. The findings of such trials would provide a more solid scientific basis for further discussions about the appropriate intake levels.

REFERENCES

- Altman, D. G. (1991). *Practical Statistics for Medical Research*. London: Chapman & Hall.
- Baird, I. M., Hughes, R. E., Wilson, H. K., Davies, J. E. W. & Howard, A. N. (1979). The effects of ascorbic acid and flavonoids on the occurrence of symptoms normally associated with the common cold. *American Journal of Clinical Nutrition* 32, 1686-1690.
<http://www.ajcn.org/cgi/content/abstract/32/8/1686>
- Bartley, W., Krebs, H. A. & O'Brien, J. R. P. (1953). Vitamin C Requirement of Human Adults. MRC Special Report Series No. 280, pp. 43-44 & 134-135. London: H. M. Stationery Office.
http://www.ltdk.helsinki.fi/users/hemila/CC/Bartley_1953_ch.pdf
- Basu, T. K. & Schorah, C. J. (1982). *Vitamin C in Health and Disease*, pp. 93-114. London: Croom Helm.
- Bendich, A & Langseth, L. (1995). The health effects of vitamin C supplementation: a review. *Journal of the American College of Nutrition* 14, 124-136 (correction: 14, 398).
<http://www.ncbi.nlm.nih.gov/pubmed/7790686>
- Bielory, L. & Gandhi, R. (1994). Asthma and vitamin C. *Annals of Allergy* 73, 89-96.
<http://www.ncbi.nlm.nih.gov/pubmed/8067602>
- Bissell, M. J., Hatie, C., Parson, D. A., Schwarz, R. I. & Soo, W. J. (1980). Ascorbic acid inhibits replication and infectivity of avian RNA tumor virus. *Proceedings of the National Academy of Sciences* 77, 2711-2715.
<http://www.pnas.org/content/77/5/2711>
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=6248860>
- Carson, M., Cox, H., Corbett, M. & Pollitt, N. (1975). Vitamin C and the common cold. *Journal of the Society of Occupational Medicine* 25, 99-102.
http://www.ltdk.helsinki.fi/users/hemila/CC/Carson_1975_ch.pdf
- Chalmers, T. C. (1975). Effects of ascorbic acid on the common cold. An evaluation of the evidence. *American Journal of Medicine* 58, 532-536.
[http://dx.doi.org/10.1016/0002-9343\(75\)90127-8](http://dx.doi.org/10.1016/0002-9343(75)90127-8)
<http://www.ncbi.nlm.nih.gov/pubmed/1092164>
- Charleston, S. S. & Clegg, K. M. (1972). Ascorbic acid and the common cold. *Lancet* 1, 1401-1402.
[http://dx.doi.org/10.1016/S0140-6736\(72\)91143-9](http://dx.doi.org/10.1016/S0140-6736(72)91143-9)
http://www.ltdk.helsinki.fi/users/hemila/CC/Charleston_1972_ch.pdf
- Clegg, K. M. & Macdonald, J. M. (1975). L-Ascorbic acid and D-isoascorbic acid in a common cold survey. *American Journal of Clinical Nutrition* 28, 973-976.
<http://www.ajcn.org/cgi/content/abstract/28/9/973>
- Denissenko, M. F., Pao, A., Tang, M. & Pfeifer, G. P. (1996). Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. *Science* 274, 430-432.
<http://www.ncbi.nlm.nih.gov/pubmed/8832894>
<http://dx.doi.org/10.1126/science.274.5286.430>
- Department of Health (1991). *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. Report on Health and Social Subjects No. 41, pp. 117-122. London: H. M. Stationery Office.
http://www.ltdk.helsinki.fi/users/hemila/experts/DH_1991.pdf
- Dykes, M. H. M. & Meier, P. (1975). Ascorbic acid and the common cold. Evaluation of its efficacy and toxicity. *Journal of the American Medical Association* 231, 1073-1079.
<http://jama.ama-assn.org/cgi/content/abstract/231/10/1073>
<http://www.ncbi.nlm.nih.gov/pubmed/1089817>
http://www.ltdk.helsinki.fi/users/hemila/reviews/Dykes_1975_ch.pdf
- Elwood, P. C., Lee, H. P., Leger, A. S., Baird, I. M. & Howard, A. N. (1976). A randomized controlled trial of vitamin C in the prevention and amelioration of the common cold. *British Journal of Preventive and Social Medicine* 30, 193-196.
<http://jech.bmj.com/cgi/reprint/30/3/193.pdf>

- <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=788820>
Englard, S. & Seifter, S. (1986). The biochemical functions of ascorbic acid. Annual Review of Nutrition 6, 365-406.
<http://dx.doi.org/10.1146/annurev.nu.06.070186.002053>
- Glazebrook, A. J. & Thomson, S. (1942). The administration of vitamin C in a large institution and its effect on general health and resistance to infection. Journal of Hygiene 42, 1-19.
http://www.ltdk.helsinki.fi/users/hemila/CP/Glazebrook_1942_ch.pdf
- Hemilä, H. (1992a). Vitamin C and the common cold. British Journal of Nutrition 67, 3-16.
<http://www.ncbi.nlm.nih.gov/pubmed/1547201>
<http://dx.doi.org/10.1079/BJN19920004>
<http://dspace2.lib.helsinki.fi:8081/dspace/handle/10250/135152> **Links added to references**
- Hemilä, H. (1992b). Vitamin C and plasma cholesterol. Critical Reviews in Food Science and Nutrition 32, 33-57.
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1992_CRC.pdf
- Hemilä, H. (1993). Vitamin C, cholesterol, and the nutritional recommendations (letter). American Journal of Cardiology 71, 503-504.
[http://dx.doi.org/10.1016/0002-9149\(93\)90498-2](http://dx.doi.org/10.1016/0002-9149(93)90498-2)
<http://dspace2.lib.helsinki.fi:8081/dspace/handle/10250/8076> **Links added to references**
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1993L.pdf
- Hemilä, H. (1994). The good and harm of vitamin C (letter). Nutrition Today 29, 49-50.
<http://dx.doi.org/10.1097/00017285-199403000-00008>
<http://dspace2.lib.helsinki.fi:8081/dspace/handle/10250/135155> **Links added to references**
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1994L.pdf
- Hemilä, H. (1996a). Vitamin C and common cold incidence: a review of studies with subjects under heavy physical stress. International Journal of Sports Medicine 17, 379-383.
<http://www.ncbi.nlm.nih.gov/pubmed/8858411>
<http://dx.doi.org/10.1055/s-2007-972864>
<http://dspace2.lib.helsinki.fi:8081/dspace/handle/10250/7983> **Links added to references**
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1996_IJSM.pdf
- Hemilä, H. (1996b). Vitamin C supplementation and common cold symptoms: problems with inaccurate reviews. Nutrition 12, 804-809.
<http://www.ncbi.nlm.nih.gov/pubmed/8974108>
[http://dx.doi.org/10.1016/S0899-9007\(96\)00223-7](http://dx.doi.org/10.1016/S0899-9007(96)00223-7)
<http://dspace2.lib.helsinki.fi:8081/dspace/handle/10250/7979> **Links added to references**
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1996_NUT.pdf
- Hemilä, H. (1997a). Vitamin C intake and susceptibility to the common cold. British Journal of Nutrition 77, 59-72.
<http://www.ncbi.nlm.nih.gov/pubmed/9059230>
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1997_BJN.pdf
- Hemilä, H. (1997b). Vitamin C and infectious diseases. In Vitamin C in Health and Disease, pp. 471-503 [L. Packer and J. Fuchs, editors]. New York: Marcel Dekker.
http://www.ltdk.helsinki.fi/users/hemila/immunity/HH_1997_MDek_immu.pdf
http://www.ltdk.helsinki.fi/users/hemila/animals/HH_1997_MDek_inf.pdf
- Hemilä, H. (1997c). Vitamin C intake and susceptibility to pneumonia. Pediatric Infectious Disease Journal 16, 836-837.
<http://dx.doi.org/10.1097/00006454-199709000-00003>
<http://dspace2.lib.helsinki.fi:8081/dspace/handle/10250/8159> **Links added to references**
http://www.ltdk.helsinki.fi/users/hemila/H/HH_1997_PIDJ.pdf
- Hemilä, H. & Herman, Z. S. (1995). Vitamin C and the common cold: a retrospective analysis of Chalmers' review. Journal of the American College of Nutrition 14, 116-123.
<http://www.ncbi.nlm.nih.gov/pubmed/7790685>
<http://www.jacn.org/cgi/content/abstract/14/2/116>

- http://www.ltdk.helsinki.fi/users/hemila/H/HH_1995.pdf
- Hennekens, C. H. & Buring, J. E. (1987). *Epidemiology in Medicine*, pp. 39-53. Boston: Little, Brown and Company.
- Kleijnen, J., Riet, G & Knipschild, P. G. (1989). Vitamine C en verkoudheid; overzicht van een megadosis literatuur (Vitamin C and the common cold: review of the megadose literature). *Nederlands Tijdschrift voor Geneeskunde* 133, 1532-1535.
<http://www.ntvg.nl/publicatie/vitamine-c-en-verkoudheid-overzicht-van-274166/volledig>
http://www.ltdk.helsinki.fi/users/hemila/reviews/Kleijnen_1989.pdf
- Light, R. J. & Pillemer, D. B. (1984). *Summing Up. The Science of Reviewing Research*. Cambridge, MA: Harvard University Press.
- Ludvigsson, J., Hansson, L. O & Tibbling, G. (1977). Vitamin C as a preventive medicine against common colds in children. *Scandinavian Journal of Infectious Diseases* 9, 91-98.
<http://www.ncbi.nlm.nih.gov/pubmed/897573>
http://www.ltdk.helsinki.fi/users/hemila/CC/Ludvigsson_1977_ch.pdf
- Marks, J. (1989). The safety of the vitamins: an overview. *International Journal for Vitamin and Nutrition Research*, Suppl. 30, 12-20.
<http://www.ncbi.nlm.nih.gov/pubmed/2507691>
http://www.ltdk.helsinki.fi/users/hemila/safety/Marks_1989.pdf
- National Research Council (1989). *Recommended Dietary Allowances*, 10th ed., pp. 115-124. Washington, DC: National Academy Press.
http://www.nap.edu/openbook.php?record_id=1349&page=115
http://www.nap.edu/openbook.php?record_id=1349&page=120
- Pitt, H. A. & Costrini, A. M. (1979). Vitamin C prophylaxis in marine recruits. *Journal of the American Medical Association* 241, 908-911.
<http://jama.ama-assn.org/cgi/content/abstract/241/9/908>
<http://www.ncbi.nlm.nih.gov/pubmed/368370>
http://www.ltdk.helsinki.fi/users/hemila/CC/Pitt_1979_ch.pdf
- Rivers, J. M. (1987). Safety of high-level vitamin C ingestion. *Annals of the New York Academy of Sciences* 498, 445-454.
<http://www.ncbi.nlm.nih.gov/pubmed/3304071>
http://www.ltdk.helsinki.fi/users/hemila/safety/Rivers_1987.pdf
- Rosenthal, R. (1978). Combining results of independent studies. *Psychological Bulletin* 85, 185-193.
<http://dx.doi.org/10.1037/0033-2909.85.1.185>
- Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin* 86, 638-641.
<http://dx.doi.org/10.1037/0033-2909.86.3.638>
- Stone, I. (1972). *The Healing Factor: Vitamin C against Disease*. New York: Grosset & Dunlap.
 See links to the book at: <http://www.ltdk.helsinki.fi/users/hemila/klenner.htm>
- Tyrrell, D. A. J., Craig, J. W., Meade, T. W. & White, T. (1977). A trial of ascorbic acid in the treatment of the common cold. *British Journal of Preventive and Social Medicine* 31, 189-191.
<http://jech.bmj.com/cgi/reprint/31/3/189.pdf>
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=479021>
- Walker, G. H., Bynoe, M. L. & Tyrrell, D. A. J. (1967). Trial of ascorbic acid in prevention of colds. *British Medical Journal* 1, 603-606.
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1841434>
- Wolf, F. M. (1986). *Meta-Analysis. Quantitative Methods for Research Synthesis*. London: Sage Publications.